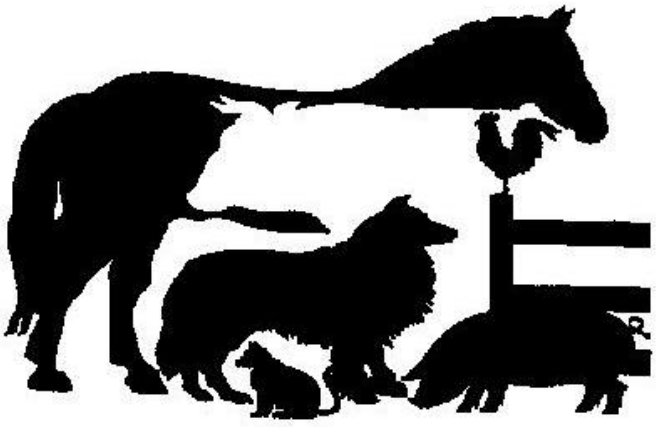
NCIE Electronic Submission Pilot Project



A Center for Veterinary Medicine Success Story

CVM started its pilot project to permit electronic submission of Notices of Claimed Investigational Exemption (NCIE) on September 8, 1997, and following an evaluation December 8, 1997, called the project a success, because it...

- Was developed in cooperation with the animal health industry, and the results have won strong industry and Center approval
- Reduced Center processing time
- Is the only completely electronic submission system developed in FDA using the internet, and the first step toward a paperless CVM

The NCIE Electronic Submission Pilot Project...Design

For the pilot project, CVM...

- Used the NCIE submissions, also known as Notices of Drug Shipment, because the anticipated number of submissions would allow a good test of the system
- Developed a standard form, allowing sponsors to merely fill in the blanks
- Selected a method for encrypting the file, so it could be transmitted securely via e-mail to CVM
- Published details of the pilot project on CVM's Home Page, so all interested sponsors had access to the information
- Asked drug sponsors to declare their intent and ability to work within project requirements
- Worked in cooperation with an industry group, the Animal Health Institute, to offer sponsors pre-project training
- Promised that electronic submissions would be reviewed using the same standards as paper submissions

The NCIE Electronic Submission Pilot Project...Evaluation

- The drug industry established a mentor program for participating companies
- Twelve animal drug sponsors registered for the project, and submitted 259 electronic submissions in the first three months
- Six review teams of CVM's Office of New Animal Drug Evaluation (HFV-112, 114, 126, 128, 133, 135) were involved in processing the submissions
- Processing time was reduced from a median of 36 days for paper submissions to 8 days for electronic submissions
- CVM reviewers and industry have found the standard format easier to process
- Drug sponsors like the ease of submitting the notices, and they like the electronic verification of receipt from CVM

The NCIE Electronic Submission Pilot Project...What's Ahead

- Over the next three months, CVM will further refine the electronic submission form by adding a comment field, check box, etc., and continue to improve internal review processing procedures
- Longer term, CVM will begin implementing electronic submission pilot projects for other reporting requirements, and
- Begin discussing requirements for electronic submission of study protocols, i.e., effectiveness, target animal safety, residue, toxicology, stability, environment, etc.

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Center for Veterinary Medicine

Electronic Submission Pilot Project Report

Three Month Report
December 8, 1997

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Background

The Center for Veterinary Medicine (CVM), in conjunction with representatives from the animal drug industry, has developed and implemented methods to accept electronic files as legal, original submissions for review. This extraordinary step was made possible by the publication of FDA's Final Rule on Electronic Records and Electronic Signatures (21 CFR Part 11) in March 1997, which set the standards for Electronic Records for FDA and its regulated industries.

The need to transfer information electronically between CVM and animal drug sponsors has been accelerated by factors within CVM:

- reduction in the number of reviewers to manage industry submissions
- reduction in paper storage capacity and expense of maintaining paper records
- need for a more timely and efficient review process

CVM's Electronic Submission Pilot Project was designed to determine the practicality of the electronic submission and review of electronic information as an alternative to the current paper-based processes. CVM started by allowing sponsors to submit Notices of Claimed Investigational Exemption (NCIE), often referred to as drug shipment notices, as e-mail attachments via the Internet. The NCIE submission was selected because of its simplicity, size, and broad use by CVM and the regulated industries.

The pilot began September 8, 1997, and an interim review was done after three months, on December 8, 1997.

> ***An evaluation meeting was held with members of industry and the Animal Health Institute's R3 Working Group on Computer Communications and Processes on December 11, 1997.*** *The consensus of that group is included in this report. This group has been invaluable as an innovative, supportive organization for this historic initiative by the Center. It is only with their support and untiring effort that this Electronic Submission initiative received the outstanding participation of the regulated industry.*

Pilot Project Overview

The pilot was designed to provide CVM and animal drug sponsors with a totally electronic submission, and to allow for review and storage of the electronic file by the Center. These procedures do not require an "official" paper archive or review copy, or production of a paper copy at any point in CVM's review process.

All participating sponsors were required to declare intent to participate and identify all Investigational New Animal Drug Files and authorized personnel (name, e-mail address), and provide the Center with a security password. The Center then assigned a User ID to each of the Sponsor's authorized personnel, after confirming ownership of the investigational files. The combination of the User ID, password and e-mail address is used to verify the electronic submission.

NCIEs are prepared by completing a word processing form with all appropriate information. A portable document format (pdf) file is created from the NCIE and password encrypted. The encrypted file is sent to the Center as an attachment to an e-mail message. Upon receipt, the e-mail message is processed automatically by confirming the sponsor and authorized sender, number of attachments and appropriate subject line. When the mail message passes these automated checks, a copy of the attached NCIE is programmatically copied to a secure network drive for archival purposes. An e-mail message is sent to a second account within CVM for the manual processing of the NCIE. During manual processing, the NCIE is opened, User ID is checked, and the submission is logged into the Center's Submission Tracking and Reporting System (STARS) database. A copy of the NCIE is then placed in an appropriate review directory, and notification is sent to the responsible reviewing organization. After CVM's receipt processing is complete, a password encrypted receipt containing pertinent assignment information is sent as an e-mail attachment to the sponsor. The Center's assignment of review responsibilities, scientific review, and final disposition follow standard policies. The final action and closure processing is accomplished using an electronic form. Any review memorandum or correspondence to the animal drug sponsor is required to be paper-based because the requirements of electronic signature have not currently been met by the Center.

Goals

The goals of the project were to gauge CVM's and industry's ability to produce, review and manage totally electronic submissions, as well as the users' comfort levels with the electronic process. Parameters such as review and transit time were to be compared with processing time of paper-based submissions. Additionally, CVM and the industry customers would assess the usability of the process.

Minimum requirements for the initiation of the project by CVM were participation by at least 5 animal drug sponsors, and a total minimum projection of at least 100 electronic NCIE submissions received during the project.

Evaluation

Twelve animal drug sponsors registered for the project. At the three-month mark, 259 electronically submitted NCIEs were received by the Center, and 213 of those were reviewed and completed. Electronic submissions were received by all Office of New Animal Drug Evaluation (ONADE) primary review branches. The Center exceeded all expectations for participation in the pilot.

A small number of initial and subsequent sporadic problems were encountered. Initial e-mail gateway incompatibilities caused errors in the processing of some sponsors' notices, and one sponsor suspended electronic submission for a time because of internal electronic gateway problems. Sponsors also attempted to include "helpful" descriptive information in the subject line of the e-mail

message that created errors in the Center's automated processing procedures. Once sponsor personnel became familiar with the requirements of the project, NCIE processing became routine. There were also occasional occurrences of multiple receipts being issued to a sponsor's NCIE submission, but this was again resolved primarily during the initial phase of the project. Other occasional errors included "unpassworded" files, incorrect password, wrong user ID, unreadable files and unreceived files. A 24-hour hotline voice mailbox at the Center was made available to participants to report any problems or unacknowledged submissions.

The processing times are presented in Table I.

Table I.

Electronic Submissions Completed During First 3 Months of Pilot
Total Processing Days

	Average	Median	Minimum	Maximum
NCIE Date to Date NCIE Received by CVM	0.8	0.0	-1	20
Date NCIE Sent by Sponsor to Date Received by CVM	0.3	0.0	-2	6
CVM Time	10.6	8.0	0	54
Date NCIE Received by CVM to Date NCIE Processed by CVM	0.9	0.0	0	7
Date NCIE Processed by CVM to Date NCIE Assigned to CVM Review Team	0.0	0.0	0	0
Date NCIE Assigned to CVM Review Team to Date of NCIE Final Action	9.8	8.0	0	54
Date NCIE Processed by CVM to Date CVM Receipt Received by the Sponsor	0.2	0.0	-7	7

The negative numbers reported as minimums are due to post-dating by the sponsor. The maximum CVM NCIE review time of 54 days was not representative of processing times, as shown by the much lower average and median, and only 8 of the 213 reviewed submissions took more than 30 calendar days in CVM review.

Two similar sets of data were extracted for paper-based submissions for comparison. One was submissions completed during the preceding 6 months for the same sponsors and INAD files participating in the pilot project (Table II), and the second was a similar set for submissions completed the preceding year during the same 3 month period (Table III). Because CVM and industry have never shared processing information, certain parameters could not be measured for the paper-based submissions. The time from the sponsor mailing the NCIE to CVM receipt was not measured for these submissions, but it is doubtful that the U.S. Postal Service (or other carriers) could have improved on a median delivery time of less than a day. Additionally, the Center's receipt was issued to participating sponsors to verify that the Center had received the submitted NCIE. It also was delivered quickly and was information useful to all drug sponsors.

Table II.

Paper Submissions Completed During the Prior 6 Months Total Processing Days				
	Average	**Median**	**Minimum**	**Maximum**
NCIE Date to Date NCIE Received by CVM	4.0	3.0	0	68
CVM Time	31.8	36.0	3	121
Date NCIE Received by CVM to Date NCIE Processed by CVM	1.6	1.0	0	5
Date NCIE Processed by CVM to Date NCIE Assigned to CVM Review Team	0.0	0.0	0	0
Date NCIE Assigned to CVM Review Team to Date of NCIE Final Action	30.1	35.0	1	119

When compared to the review performance for previous 6 months, the Center decreased processing and review time to less than a third of the time required for paper-based submissions when using either average or median as the comparison standard. The average CVM review time decreased from 31.8 days to 10.6 days, and median review time was reduced from 36 to 8 days.

Table III.

Paper Submissions Completed During 1996 for the Same Period Total Processing Days				
	Average	**Median**	**Minimum**	**Maximum**
NCIE Date to Date NCIE Received by CVM	3.2	2.0	0	17
CVM Time	27.5	23.0	2	132
Date NCIE Received by CVM to Date NCIE Processed by CVM	1.5	1.0	1	4
Date NCIE Processed by CVM to Date NCIE Assigned to CVM Review Team	0.0	0.0	0	0
Date NCIE Assigned to CVM Review Team to Date of NCIE Final Action	26.0	22.0	1	131

Staffing levels have decreased over the past year and have impacted on the resources available for review of information submitted by animal drug sponsors. Even when compared with the performance for a similar period the previous year, an improvement in review time was realized and reviews were completed in less than 40% of review time for paper-based submissions. The average review time decreased from 27.5 days to 10.6 days, and median review time decreased from 23 days to 8 days.

Definitions Used in Tables

NCIE Date – The date used in the body of the NCIE (incorporated into the NCIE by the sponsor).

Date NCIE Received by CVM – The date the e-mail message with the NCIE attachment was received by the automated mail processing account at CVM. This account was active 24 hours a day, and was not restricted to "business" days.

Date NCIE Sent by Sponsor – The date (reported by the sponsor) that the NCIE was successfully sent to CVM. Although there were occasions that the sponsor had to re-send a file, the number of times the file had to be re-sent is captured in another field.

Date NCIE Processed by CVM – The date the NCIE was initially processed by CVM. This included logging the submission into the STARS tracking system, making a "review" copy of the file, and sending a receipt to the sponsor.

Date CVM Receipt Received by the Sponsor - The date (reported by the sponsor) the sponsor received CVM's notification of receipt of the NCIE.

Date NCIE Assigned to CVM Branch – The date the electronic Document Control Unit notified the reviewing organization that the NCIE was available for assignment to a reviewer.

Date of NCIE Final Action – The date CVM completed review of information in the NCIE and filed the NCIE and any review material in the official file.

CVM Time (days) = Date of NCIE Final Action *minus* **Date NCIE Received by CVM**

Time to CVM (days) = Date NCIE Received by CVM *minus* **Date NCIE Sent by Sponsor**

Time from CVM (days) = Date CVM Receipt Received by the Sponsor *minus* **Date NCIE Processed by CVM**

Evaluation Data

CVM Data

The CVM Submission Tracking and Reporting System database (STARS) was used as a source of all CVM information. Data were entered into STARS at the receipt and closure of the submission processing according to CVM's standard procedures. Database queries were used to extract the data into a spreadsheet for evaluation.

Sponsor Data

Information from the participating sponsors was transmitted to CVM in a variety of formats and imported into a spreadsheet and matched with corresponding records for purposes of this report.

Additional Comments

E-mail messages containing information such as corrections, data files, questions, and changes to original Letters of Intent sent to the e-CVMDCU were processed as errors because they did not contain the agreed upon information in the subject line of the e-mail. This has been a minor problem for the pilot. The guidance document needs to be modified to clarify that only acceptable electronic submissions should be sent to the e-CVMDCU address, and general questions and information should be sent to an identified contact in CVM. When other kinds of submissions are to be accepted electronically, acceptable subject lines will be added to the automated processing system.

Sponsor's file naming conventions followed a variety of conventions. Some did not follow the 8.3 convention requested at the pilot training, but those directions were not detailed in the guidance document. Since this will be a fatal flaw in new CVM automated processing, the guidance document should be explicit on this point. In addition, we should notify all participating sponsors of the necessity of adherence to an 8.3 file naming convention.

Sponsor's Letters of Intent were required to be submitted to all the investigational files owned by the sponsor. This is far in excess of the quality check required of paper submissions, but the Center believed this quality assurance step was necessary. The Letter of Intent logged into each investigational file was very labor intensive. If we are to expand the electronic submission to other types of submissions and other participants, we need a simpler and less resource intensive registration process. In addition, sponsors were unsure of the notification procedure when a new INAD was established after the initial Letter of Intent was processed by the Center.

NCIE form for submission of information as defined in the Electronic Submission of NCIEs Guidance Document was determined to be too restrictive. On occasion, there was important and crucial information that needed to be submitted to the Agency, but there was no place for it in the form. Because there was no free text comment field, sponsors were confused about how to transmit this information. There were also cases of drug shipments being cancelled or notices needing to be corrected. Since we distributed the form as a word processing form, some sponsors were hesitant or unable to make ***any*** changes to the initial form. The form will be amended to include these features. After the NCIE form is finalized, it should replace the current forms available through the CVM Home Page.

Electronic compatibility between the Center and participating sponsors was tested prior to the initiation of submission of the NCIEs. Access to the Electronic Submission Pilot Project and transmittal of the documents as encrypted and protected documents required cooperation and coordination of the IT staffs and capabilities between both the Center and sponsors. Most of these minor problems were corrected with minimum difficulty. For one sponsor, the solution to transmitting to the Center was to use a commercial Internet Service Provider instead of the company's business e-mail gateway.

Sponsors' comments were generally positive. The encryption standard was viewed as adequate and more secure than a facsimile that many sponsors currently use to transmit information. The receipt was viewed as very favorable, and there were requests for a similar process in paper. Some changes to the NCIE form were requested, and some sponsors processed both paper and electronic for their companies' records, which increased their workload. A request was made for a format that would facilitate electronic submissions of export notices. The most overwhelming comment was "When can we submit protocols, FOI summaries and other information?"

Suggestions for Modifications to the Pilot

NCIE Form Modifications

- Additional free text block for comments and non-routine information.
- Checkbox for Original, Revised, or Cancelled NCIE
- Instructions for completing form and emphasis on CVM HFV-### address
- Official FDA form number and date of form version
- Header Information on page 2 of form

CVM Processing Modifications

- Include sponsor source file name in CVM database
- Fatal flaw for non-adherence to 8.3 file naming
- De-encrypt files programmatically prior to storing for archival purposes
- Simplify Electronic Submission registration process

Continue Pilot to evaluate effects of modifications to NCIE form and CVM processing, but require only error reporting by the participating sponsors.

Recommendations

Since the electronic submission of NCIEs *reduced CVM review time to less than a third* when compared to paper-based submissions, the Center should expand its Electronic Submission initiative. Several items should be addressed as soon as possible.

Finalize electronic submission of NCIEs

After monitoring the Electronic Submission pilot for an additional 3 months to evaluate the changes to processing, the Center should officially adopt the procedures and finalize the guidance document for NCIE electronic submissions.

Adapt Electronic Submission Pilot Form as CVM's official form

The standardization of the electronically submitted NCIEs makes review of the statutorily required information easier because the same information is always located in the same place on the form. The Center should proceed as soon as possible to obtain approval from OMB of the form and distribute it through the CVM Home Page on the World Wide Web. This applies to both the paper and electronic based forms.

Identify next electronic submission pilot

Because the process for guidance document preparation and acceptance is so lengthy, the next type of submission pilot should be identified as soon as possible. It would seem a fairly easy step to expand the same technology to USDA slaughter reports, sponsor animal slaughter notifications, other routine reporting requirements as well as meeting agendas, meeting minutes, and draft FOI summaries. Substantial sponsor and CVM interest exists in developing a pilot for protocol submission and review, and the Center should move toward identifying requirements for electronic submission of study protocols.

Inspect CVM electronic records management

CVM has taken the first step to "go completely electronic." This means records management and storage systems in the Center must adhere to the standards of 21 CFR 11. An inspection by Agency personnel should be scheduled as soon as possible after the midterm modifications to assure the processing procedures are completed.

Transfer electronic submission processing to CVM's Document Control Unit

The developmental group has overseen the submission processing for the pilot project to facilitate quality control during the initial stages. This function should be transferred to the CVM Document Control Unit after the next evaluation period.

Set standards for electronic copies of paper submissions

The Center was working previously on guidance in this area. Those standards should be updated, if necessary, and finalized. Also storage of those electronic copies within CVM should be addressed.

Reference Documents

CVM Guidance for Industry #59 (Pilot Project) “Submitting a Notice of Claimed Investigational Exemption in Electronic Format to CVM via E-Mail”, dated June 16, 1997. (http://www.cvm.fda.gov/fda/infores/NCIE/guidance.pdf)

Federal Register Publication “Electronic Records; Electronic Signatures; Final Rule” and “Electronic Submissions; Establishment of Public Docket; Notice”, dated March 20, 1997, 21 CFR Part 11, FR Vol.62, No.54, Page 13430-13466. (May be located using Federal Register On-line Search at http://www.access.gpo.gov/su_docs/aces/aces140.html)

FDA Docket #92S-0251 “Electronic Submission; Basic Information Regarding Submission of Notices of Claimed Investigational Exemption to Center for Veterinary Medicine”, dated September 3, 1997. (http://www.fda.gov/dockets/dockets/92s0251/m1.pdf)